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Introduction

Multiple emulsions, in particular water-in-oil-in-water (w/o/w) emulsions, are promising systems for encapsulation and controlled delivery of drugs. We developed a new emulsifier, a poly(dimethylsiloxane)-b-poly(dimethylaminoethylmethacrylate) (PDMS-b-PDMAEMA) amphiphilic copolymer, capable of stabilizing multiple emulsions in one mixing step over long times. This polymer is stimuli responsive, allowing the formation of direct, inverse and w/o/w emulsions depending on the pH and ionic strength. It is then possible to consider the controlled release of a compound encapsulated in the inner water droplets.

However it is highly desirable to both form monodisperse emulsions for reaching a reliable control of the delivery and differentiate the inner water phases carrying the cargo from the external water phase for avoiding tedious washing steps. For all these reasons microfluidics was considered as a promising tool and is shown here to provide first promising results.

Experimental

Polymer synthesis: In a first step[1], hydroxy-terminated PDMS is functionalized with bromide thanks to esterification with bromoisobutyryle bromide. In a second step[2], the controlled polymerization of DMAEMA is realized by ATRP. The polymer is then characterized by ^{1}H NMR and size-exclusion chromatography.

Microfluidics: Molds with the correct circuit design are made by soft lithography[3]. PDMS Sylgard 184 and its crosslinking agent are mixed together, degassed, casted in the mold and cured overnight at 65°C before use. Chips are then peeled, punched and plasma bonded on PDMS or glass substrate. In some cases, a solution of either hydrophilic or hydrophobic compound is injected right after the bonding to realize a covalent surface treatment of the channels.

Formation of the emulsions: The biocompatible oil phase used here is either Miglyol 812® or isopropyl myristate. The aqueous phase is deionized water whose pH was adjusted by adding hydrochloric acid or sodium hydroxide. The ionic strength is set by the amount of sodium chloride dissolved in water. The two phases are put in contact for 24h before being injected in microfluidic chips with syringe pumps, or before being mixed by Ultra-Turrax for 40s at 24000rpm for making emulsions outside of microfluidic set-ups.

Results and discussion

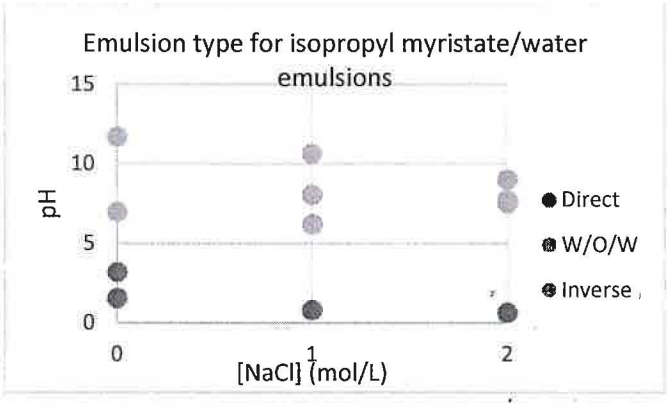
PDMS-b-PDMAEMA is able to stabilize emulsions at different pH and ionic strengths. Since amine units of DMAEMA can be charged, the PDMAEMA block is very hydrophilic at low pH, and should stabilize preferentially oil-in-water droplets. On the contrary, at higher pH

or ionic strength the polymer is more hydrophobic and inverse emulsions should be formed. In intermediate conditions, both interfaces can be stabilized and w/o/w emulsions are observed in a precise range of parameters. The results obtained when making the emulsions with Ultra-Turrax are consistent with this reasoning (Fig 1).

We tried to compare these results with droplets formation in microfluidics. We used a flow focusing junction as a droplet generator. The surface of the channels is rendered hydrophilic or hydrophobic by an appropriate coating to allow the formation of direct emulsions in the first case and inverse emulsions in the second.

It was possible to form droplets of the two kinds for different pHs and ionic strengths (Fig 2). In particular, stable direct and inverse emulsions were obtained at a pH where w/o/w emulsions only were formed with Ultra-Turrax.

The next step is the formation of w/o/w emulsions. For that purpose we first generate water droplets in oil before encapsulating the oil phase with water. Several strategies were studied: the use of two separate chips, the first hydrophobic and the second hydrophilic, or the use of a unique chip where part of the channels is hydrophobically treated and the other part is made hydrophilic. First results of both strategies will be presented.



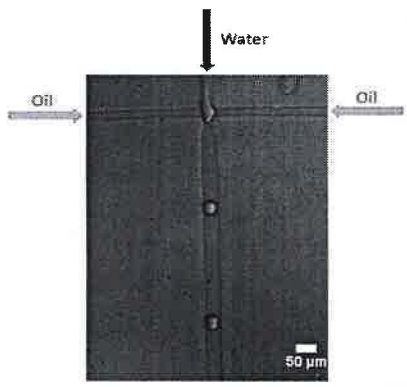


Fig 1: *(left) Type of the water/isopropyle myristate emulsions formed with Ultra-Turrax in function of pH and [NaCl]* – **Fig 2:** *(right) Example of droplet formation in microfluidics – water-in-oil droplet – water flow rate=0.035µL/min – oil flow rate=1µL/min*

Conclusions

We developed a very promising system for the formation of stimulable multiple emulsions which can be used for drug delivery. To ensure a perfect control of the size of the droplets, and of the amount of water encapsulated in the double emulsions, these emulsions were made in microfluidic chips.

References

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Water-in-oil-in-water emulsions are promising systems for encapsulation and controlled delivery of hydrophilic drugs. We developed a biocompatible and stimulable copolymer able to stabilize direct, inverse or double emulsions depending on the pH and the ionic strength of the aqueous phase. By changing pH or temperature, the double emulsion can be destabilized and thus an encapsulated drug released. Such emulsions are made in PDMS microchips allowing a perfect control of their dispersity.